

# Noise in nanopore sensors: Sources, models, reduction, and benchmarking

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## ABSTRACT

Label-free nanopore sensors have emerged as a new generation technology of DNA sequencing and have been widely used for single molecule analysis. Since the first  $\alpha$ -hemolysin biological nanopore, various types of nanopores made of different materials have been under extensive development. Noise represents a common challenge among all types of nanopore sensors. The nanopore noise can be decomposed into four components in the frequency domain ( $1/f$  noise, white noise, dielectric noise, and amplifier noise). In this work, we reviewed and summarized the physical models, origins, and reduction methods for each of these noise components. For the first time, we quantitatively benchmarked the root mean square (RMS) noise levels for different types of nanopores, demonstrating a clear material-dependent RMS noise. We anticipate this review article will enhance the understanding of nanopore sensor noises and provide an informative tutorial for developing future nanopore sensors with a high signal-to-noise ratio.

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## 1. Introduction

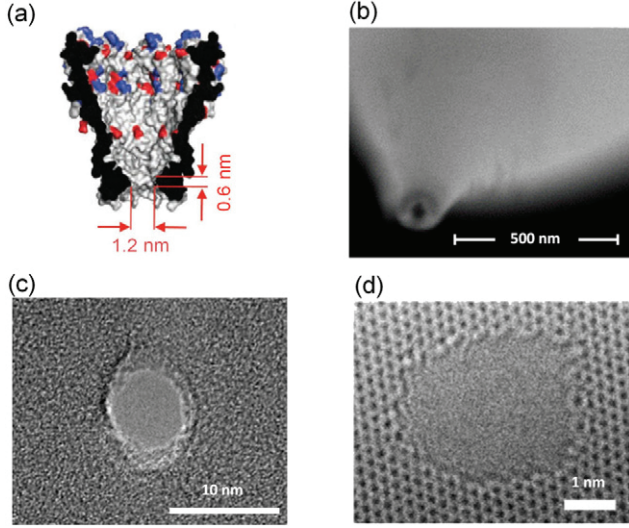
Nanopores have emerged as a promising label-free biosensor for analyzing various kinds of biomolecules such as DNA,<sup>1,2</sup> RNA, and proteins.<sup>3</sup> A nanopore sensor is often operated by applying a constant voltage across two chambers to electrophoretically drive charged biopolymers through a nanoscale hole. The readout is an ionic current trace with individual dips corresponding to a single molecule translocation, usually called an event. The ionic current shape (e.g., current blockage magnitude, shape, and duration) of each event provides the basis for interpreting the molecule length, shape, charge, and reactivity of the nanopore surface.<sup>4–27</sup> Various types of nanopores are currently under investigation (Fig. 1). The nanopore concept was first demonstrated with the protein pore  $\alpha$ -hemolysin,<sup>28</sup> a member of the biological pore family that also includes MspA porin pores.<sup>29</sup> Biological nanopores have been successfully commercialized in Oxford Nanopore DNA sequencer.<sup>30,31</sup> In addition to the pore-forming proteins, solid-state nanopores have also been extensively studied in the past decade due to their mechanical robustness, tunable size, thermal robustness, and

integration potential.<sup>32,33</sup> The solid-state nanopore family includes membrane materials such as  $\text{SiN}_x$ ,<sup>13,34,35</sup> graphene,<sup>36</sup> glass nanopores (nanopipette),<sup>37</sup> and polymer nanopores.<sup>38</sup> While solid-state nanopores have obvious advantages over their biological counterparts due to flexibility in tuning the geometry and surface properties, the noise performance of solid-state nanopores is often worse than their biological counterparts.<sup>39</sup> In addition, there is a large variation in the noise of different types of nanopores.

Since the signal in the nanopore experiment is often very small, the noise represents a significant challenge that would severely limit the nanopore sensor's sensitivity and reliability. In general, the nanopore noise power spectral density (PSD) can be decomposed into  $1/f$  noise, white noise, dielectric noise, and amplifier noise,<sup>33</sup> each dominating at different frequencies. While the nanopore noise has been extensively studied and the mechanisms previously proposed,<sup>43–46</sup> a systematic review and comparison of the noise performances of different nanopore types are needed.

In this work, we reviewed and summarized the physical models, origins, and reduction methods for each of these noise components. For the first time, we calculated and benchmarked the root mean square (RMS) values for different types of nanopores. There is a clear material-dependent intrinsic nanopore noise performance. The correlation of the noise performance to the nanopore materials may provide

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**Fig. 1.** Structures of different nanopore types. (a) MspA protein nanopore<sup>40</sup> (Reprinted by permission from [Springer Nature Customer Service Centre GmbH]; [Springer Nature] [Nature Biotechnology] (Reading DNA at single-nucleotide resolution with a mutant MspA nanopore and phi29 DNA polymerase, Manrao EA et al.), [COPYRIGHT] (2012)). (b) Glass nanopore<sup>41</sup> (Reprinted with permission from [Nouri R, Tang ZF, Guan WH. Calibration-free nanopore digital counting of single molecules. *Analytical Chemistry* 2019;91(17):11178–11184.]. Copyright (2019) American Chemical Society.). (c) SiN<sub>x</sub> nanopore. (d) Graphene nanopore<sup>42</sup> (Reprinted by permission from [Springer Nature Customer Service Centre GmbH]; [Springer Nature] [Nature Communications] [Tailoring the hydrophobicity of graphene for its use as nanopores for DNA translocation, Schneider GF et al.], [COPYRIGHT] (2013)).

alternative insight into understanding and controlling the nanopore noise. We anticipate this review article would provide an informative tutorial into developing future nanopore sensors with improved signal-to-noise ratio (SNR).

## 2. Nanopore noise analysis and model

There are generally two approaches for analyzing the nanopore noise. One approach is to directly calculate the RMS value in the time domain,<sup>47–49</sup>

$$I_{\text{rms}} = \sqrt{\Delta I^2(t)} \quad (1)$$

where  $\Delta I(t)$  represents the fluctuation of the current  $I(t)$  deviating from its mean value.

The RMS current can be directly compared to the molecule translation signal for evaluating the SNR,<sup>50</sup>

$$\text{SNR} = \Delta I_{\text{ionic}} / I_{\text{rms}} \quad (2)$$

where  $\Delta I_{\text{ionic}}$  represents the current blockage amplitude when the charged biopolymers pass through the nanopore.

The other approach is frequency domain analysis of the PSD,<sup>51</sup> which can be derived as,

$$S_I(f) = \frac{1}{2T} \lim_{T \rightarrow \infty} \left| \int_{-T}^T \Delta I(t) e^{-2\pi i f t} dt \right|^2 \quad (3)$$

The noise RMS can be related to the noise PSD as,

$$I_{\text{rms}} = \text{sqrt} \left( \int_{f_1}^{f_2} S_I(f) df \right) \quad (4)$$

Generally, the noise PSD can be decomposed into four components as,

$$S_I(f) = S_F(\propto 1/f) + S_W(\propto f^0) + S_D(\propto f) + S_A(\propto f^2) \quad (5)$$

where  $f$  is the frequency;  $S_F$ ,  $S_W$ ,  $S_D$ , and  $S_A$  represent the PSD of  $1/f$  noise, white noise, dielectric noise, and amplifier noise, respectively.<sup>33</sup>

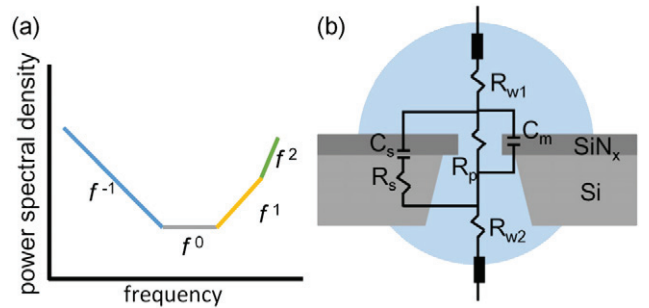
Fig. 2(a) summarizes the general characteristics of the nanopore noise PSD.<sup>50</sup> At low frequencies, noise PSD is mainly contributed to by the  $1/f$  noise. At moderate frequencies, dielectric noise due to dielectric thermal loss starts to become a major source of the noise. At high frequencies, noise is dominated by the amplifier noise. The white noise is spread uniformly at different frequencies and could be overwhelmed by the  $1/f$  and dielectric noise, while being unaffected by the noise PSD.<sup>44,52</sup> The transition points where each noise source starts to dominate could vary tremendously among different experiments.<sup>39,52–54</sup> Fig. 2(b) shows the equivalent circuit model for describing the noise component in the nanopore sensors.<sup>55</sup> In Sections 3 to 6, we review and summarize the general characteristics of each of these noises and discuss approaches for noise reduction.

## 3. $1/f$ noise

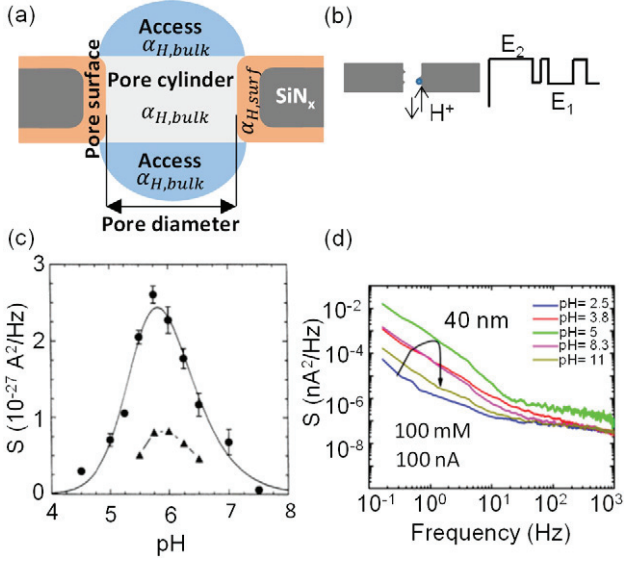
### 3.1. $1/f$ noise origin

A widely accepted theory of  $1/f$  noise is that its spectra consists of a set of Lorentzian noises that come from a group of random telegraph noises (RTNs).<sup>56</sup> This model was verified by magnetization current experiments.<sup>57</sup> Specifically, the observed  $1/f$  noise is the superposition of many discrete RTNs.  $1/f$  noise often dominates the total noise at frequencies  $< 1$  kHz and is the most widely studied.<sup>39,51,58,59</sup>

The exact origin of the  $1/f$  noise remains controversial. A variety of  $1/f$  noise mechanisms have been proposed, including the channel's opening-closing process,<sup>60</sup> structural flexibility of the nanopore pore walls,<sup>61</sup> nanobubbles,<sup>62,63</sup> incomplete hydrophilicity of the nanopore surface,<sup>64</sup> cooperative fluctuations on ion motion along a confined space,<sup>65</sup> surface reversible adsorption of ions combined with the ions' long-lasting excursions in the reservoirs,<sup>66</sup> carbon contaminants surrounding the nanopore surface during transmission electron microscopy (TEM) drilling,<sup>67</sup> and mechanical vibrations.<sup>68–72</sup> These mixed models strongly indicate the  $1/f$  noise stems from many different sources.



**Fig. 2.** Noise PSD distribution and equivalent circuit of the nanopore. (a) Noise PSD on a log-log scale (redrawing based on reference<sup>50</sup>) (Reprinted from Analytica Chimica Acta, 1061, Hartel AJW et al., High bandwidth approaches in nanopore and ion channel recordings - A tutorial review, 13–27, Copyright (2019), with permission from Elsevier.). (b) Structure of simplified model circuits of the pores (redrawing based on reference<sup>55</sup>) (Reprinted with permission from [Waggoner PS, Kuan AT, Polonsky S, Peng HB, Rossnagel SM. Increasing the speed of solid-state nanopores. *Journal of Vacuum Science & Technology B* 2011;29(3):032206.]. Copyright [2011], American Vacuum Society.). Here  $R_{w1}$  and  $R_{w2}$  are the resistance between the electrodes and electrolytes.  $R_p$  represents the resistance of the pore structure.  $R_s$  represents the electrical path between the substrate and the dielectric layer.  $C_s$  and  $C_m$  are the substrate capacitance and suspended membrane capacitance.



**Fig. 3.** Sources of noise distribution in a nanopore and surface effect on  $1/f$  noise. (a) Scheme of a solid-state nanopore (redrawing based on reference<sup>59</sup>) (Republished with permission of Nanotechnology, from [1/f noise in solid-state nanopores is governed by access and surface regions, Fragasso A et al., 30, 395202 2019]; Permission conveyed through Copyright Clearance Center, Inc.). (b) Simple model of a reversible ionization reaction of groups on the surface of a nanopore channel (redrawing based on reference<sup>73</sup>); Surface charge effect on PSD of different nanopores: (c) Biological nanopore<sup>73</sup> (Reprinted figure with permission from [Bezrukov SM et al., Physical Review Letters, 70, 2352–2355 1993.] Copyright (1993) by the American Physical Society.). (d) Solid-state nanopore ( $\text{SiN}_x$  nanopore)<sup>74</sup> (Reprinted with permission from [Wen C, Zeng SS, Arstila K, et al. Generalized noise study of solid-state nanopores at low frequencies. ACS Sensors 2017;2(2):300–307.]. Copyright (2017) American Chemical Society.).

Among all of the existing models for  $1/f$  noise, the most widely studied is the conductance fluctuation model. To understand this model, the nanopore structure is divided into three parts, the pore-surface, pore-cylinder, and access region,<sup>59</sup> as shown in Fig. 3(a). The whole nanopore resistance can be modeled as,<sup>59</sup>

$$R_{\text{tot}} = R_{\text{access}} + (R_{\text{p,bulk}} // R_{\text{p,surf}}) \quad (6)$$

in which  $(R_{\text{p,bulk}} // R_{\text{p,surf}})$  represents the channel resistance ( $R_{\text{pore}}$ ) in the nanopore; the “//” symbol means the parallel connection of the two resistors;  $R_{\text{access}}$  is the nanopore access resistance. The  $1/f$  noise PSD can, therefore, be expressed as,<sup>59</sup>

$$S_{I,\text{tot}} = \frac{V^2}{f R_{\text{tot}}^4} \left[ \frac{\alpha_{\text{H,bulk}} R_{\text{access}}^2}{N_{\text{access}}} + \left( \frac{\alpha_{\text{H,bulk}}}{R_{\text{p,bulk}}^2 N_{\text{p,bulk}}} + \frac{\alpha_{\text{H,surf}}}{R_{\text{p,surf}}^2 N_{\text{p,surf}}} \right) R_{\text{pore}}^4 \right] \quad (7)$$

in which  $\alpha_{\text{H,bulk}}$  is the bulk Hooke constant and  $\alpha_{\text{H,surf}}$  is the surface Hooke constant;  $N_{\text{access}}$ ,  $N_{\text{p,bulk}}$  and  $N_{\text{p,surf}}$  are the charge carrier numbers in the access, pore-cylinder, and pore-surface region, respectively. Based on the conductance fluctuation model (Eq. (7)), the  $1/f$  noise can be attributed to the fluctuation of the surface and bulk conductance. In the following section, we will separately discuss these two effects.

### 3.1.1. Surface effect

Surface charges exist at the nanopore walls<sup>46,73,75</sup> and their fluctuation may induce the surface conductance change in the nanopore. Fig. 3(b) shows a simple model of a reversible ionization reaction on the nanopore wall surface. In this model,<sup>73</sup>  $E_1$  and  $E_2$  represent two different energy states at a single point on the nanopore walls, which corresponds to the association and dissociation of the protons. The

probability of state  $E_1$  and  $E_2$  were given by,

$$P_1 = \frac{\tau_1}{\tau_1 + \tau_2} = \frac{1}{1 + 10^{pK - pH}}, P_2 = 1 - P_1 \quad (8)$$

Here,  $pK$  represents the log form of the equilibrium constant;  $pH$  represents the measure of the acidity or basicity of a solution;  $\tau_1$  and  $\tau_2$  represent the mean time spent in states  $E_1$  and  $E_2$ , respectively. The PSD of the Lorentzian RTN noise associated with site  $j$  can be represented as,

$$S_j(f) = \frac{4(\Delta i_{1,2})^2 \tau^2}{(\tau_1 + \tau_2) [1 + (2\pi f \tau)^2]} \quad (9)$$

in which  $\tau = \tau_1 * \tau_2 / (\tau_1 + \tau_2)$ . For sufficiently large numbers of RTN noise, a macro  $1/f$  spectrum could appear.<sup>56</sup> A previous molecular dynamics (MD) simulation demonstrated excellent agreement to the adsorption-desorption model predictions.<sup>66</sup>

The surface charge fluctuation can be affected by the pH,<sup>73,74</sup> ionic concentration,<sup>46</sup> and film material.<sup>51</sup> From the perspective of pH, Fig. 3(c) and (d) show the nanopore PSD under different pH values, for biological and  $\text{SiN}_x$  nanopores, respectively. Both PSDs showed the same trend with pH; the peak PSD appears at intermediate pH values, corresponding to the material's point of zero charges. From the perspective of ionic concentration, the normalized PSD ( $S_G/G^2$ ) increases with decreasing concentrations<sup>44,46</sup> as the nanopore size is comparable to or even smaller than the Debye length at low ionic concentrations. As a result, ions in the nanopore will be more significantly affected by surface charge fluctuations. From the perspective of the material, the different materials have different surface functional groups with varying densities of charges. As a result, nanopores made of different materials will have different  $1/f$  noise properties.<sup>51</sup> For example, the  $1/f$  noise of a  $\text{SiN}_x$  nanopore is usually much larger than that of a biological nanopore<sup>39</sup> or glass nanopore.<sup>76</sup>

Hydrophilicity is another important surface effect that could affect the  $1/f$  noise. It was previously hypothesized that nanobubbles can form at a nanopore surface that produces high  $1/f$  noises when the surface is hydrophobic.<sup>62,63</sup>

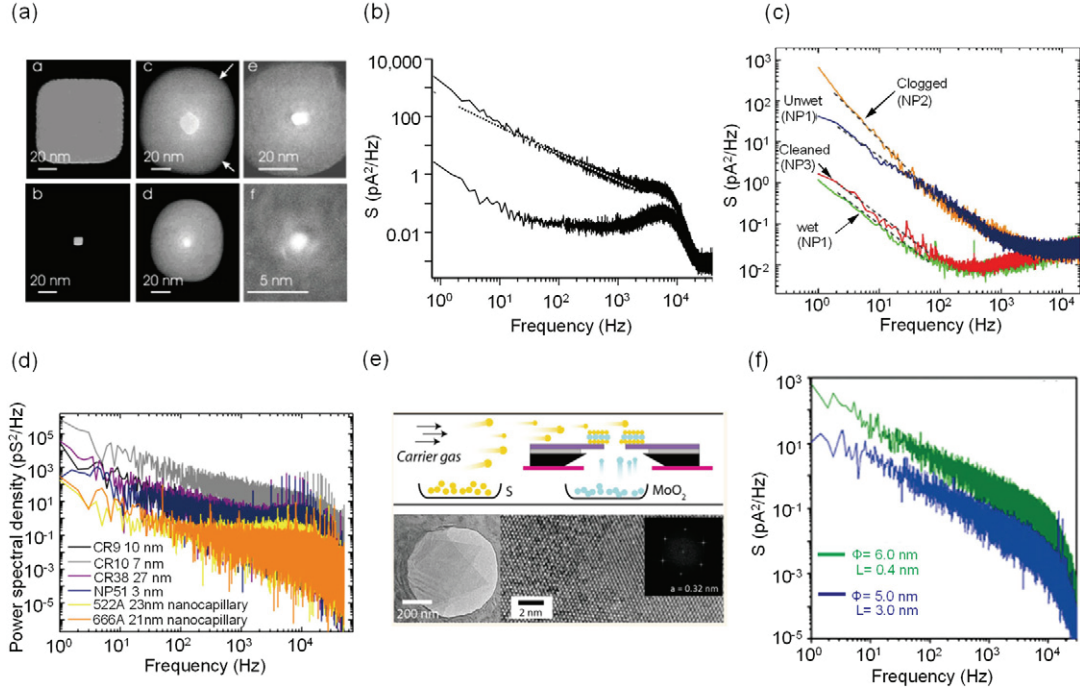
### 3.1.2. Bulk effect

The bulk and access region of the nanopore is another important source for the  $1/f$  noise (Eq. (7)).<sup>59</sup> The bulk effect mostly comes from ionic mobility fluctuation. The mobility fluctuation can be caused by (1) ionic crowding due to larger ion concentrations in the pore under a voltage bias for a single rectifying conically-shaped nanopore; (2) electrostatic interactions between passing ions and pore walls; and (3) vortices formations at the pore entrance due to the conical geometry.<sup>77</sup> The exact mechanism remains unclear, as illustrated by a variety of models. For example, Fragasso et al. ascribed the carrier free path length fluctuations as the origin for ion mobility fluctuations.<sup>59</sup> Tasserit et al. hypothesized the confinement-induced cooperative fluctuation of ion mobility leads to  $1/f$  noise.<sup>65</sup> The ionic concentration and nanopore geometry will also affect the mobility fluctuations. Wen et al. argued that the bulk region of the nanopore structure plays a dominant role in noise at high concentrations.<sup>74</sup>

### 3.2. Reducing the $1/f$ noise

For surface-related  $1/f$  noise sources, improvements in the hydrophilicity are the most common practice (Fig. 4), which can be achieved by atomic layer deposition (ALD) of  $\text{TiO}_2$ <sup>78</sup> or  $\text{Al}_2\text{O}_3$ <sup>79</sup> (Fig. 4(a) and (b)), piranha cleaning,<sup>39</sup> oxygen plasma,<sup>39</sup> and pulsed voltage treatment<sup>64</sup> (Fig. 4(c)). Among these methods, ALD deposition is capable of reducing the surface charge density, which can also be achieved by changing the pH. Finally, using alternative nanopore materials<sup>76</sup> (Fig. 4(d)) can also reduce the surface-related  $1/f$  noise.





**Fig. 4.** Methods for reducing  $1/f$  noise. (a) Depositing  $\text{Al}_2\text{O}_3$  by ALD and (b) reducing effect, here the higher line represents an untreated chip and the lower line represents a treated chip<sup>79</sup> ((a) and (b) reprinted with permission from [Chen P, Mitsui T, Farmer DB, Golovchenko J, Gordon RG, Branton D. Atomic layer deposition to fine-tune the surface properties and diameters of fabricated nanopores. *Nano Letters* 2004;4(7):1333–1337.]. Copyright (2004) American Chemical Society.). (c) Hydrophilic treatment using a “zapping” method<sup>64</sup> (Republished with permission of Nanotechnology, from [Precise control of the size and noise of solid-state nanopores using high electric fields, Beamish E et al., 23, 405301 (7pp) 2012]; Permission conveyed through Copyright Clearance Center, Inc.). (d) Power spectral density comparing between glass and  $\text{SiN}_x$  nanopore<sup>76</sup> (Reprinted with permission from [Steinbock LJ, Bulushev RD, Krishnan S, Raillon C, Radenovic A. DNA translocation through low-noise glass nanopores. *ACS Nano* 2013;7(12):11255–11262.]. Copyright (2013) American Chemical Society.). (e) Direct and scalable deposition of low-noise  $\text{MoS}_2$  membranes by a CVD method<sup>80</sup> (Reprinted with permission from [Waduge P, Bilgin I, Larkin J, et al. Direct and scalable deposition of atomically thin low-noise  $\text{MoS}_2$  membranes on apertures. *ACS Nano* 2015;9(7):7352–7359.]. Copyright (2015) American Chemical Society.). (f) Comparison of the noise power spectrum density of single- and multi-layer graphene nanopores<sup>68</sup> (Republished with permission of Nanotechnology, from [Noise and its reduction in graphene-based nanopore devices, Kumar A et al., 24, 495503 (7pp) 2013]; Permission conveyed through Copyright Clearance Center, Inc.).

For bulk-related  $1/f$  noise sources, decreasing the mobility fluctuation can be achieved by increasing the concentration of electrolyte or by choosing nanopores with a large pore diameter. The bulk-related  $1/f$  noise can be improved by enhancing the film mechanical stability (Fig. 4(e)),<sup>80</sup> increasing the film thickness (Fig. 4(f)),<sup>68</sup> and decreasing the film free-standing area.<sup>71</sup> Enhancing the film mechanical stability is of particular importance to reducing the noise of 2D material nanopores.

## 4. White noise

### 4.1. White noise origin

A key characteristic of white noise is the PSD is independent of the frequency. There are two sources for the white noise, thermal noise, and shot noise.<sup>59</sup> The general white noise can be written as,

$$S_{I,\text{white}} = S_{I,\text{thermal}} + S_{I,\text{shot}} = 4KTG + 2qI \quad (10)$$

where  $G$  is the conductance,  $K$  is the Boltzmann constant,  $T$  is the temperature,  $q$  is the elementary charge, and  $I$  is the current. The thermal noise (Johnson noise) arises from thermal fluctuations in the charge carriers (i.e., ions in the nanopore sensors). The shot noise (Poisson noise) normally occurs when there is a potential barrier. In the nanopore sensors, the  $\text{Ag}/\text{AgCl}$  interface is an example of a potential barrier. When the electrons/ions cross that barrier, shot noise can be produced.<sup>43</sup> Note that a pure resistor normally does not produce shot noise since there is no potential barrier. Both thermal and shot noises are inherent to a real system, representing fundamental limitations (lower noise floor) in making sensitive measurements.

### 4.2. Reducing the white noise

One possible method to decrease the thermal noise is to decrease the conductance by decreasing the charge carriers' concentration or the pore size.<sup>43</sup> Increasing the channel length of the nanopore could also decrease the thermal noise, however, this would reduce the sensitivity of the pore.<sup>81</sup>

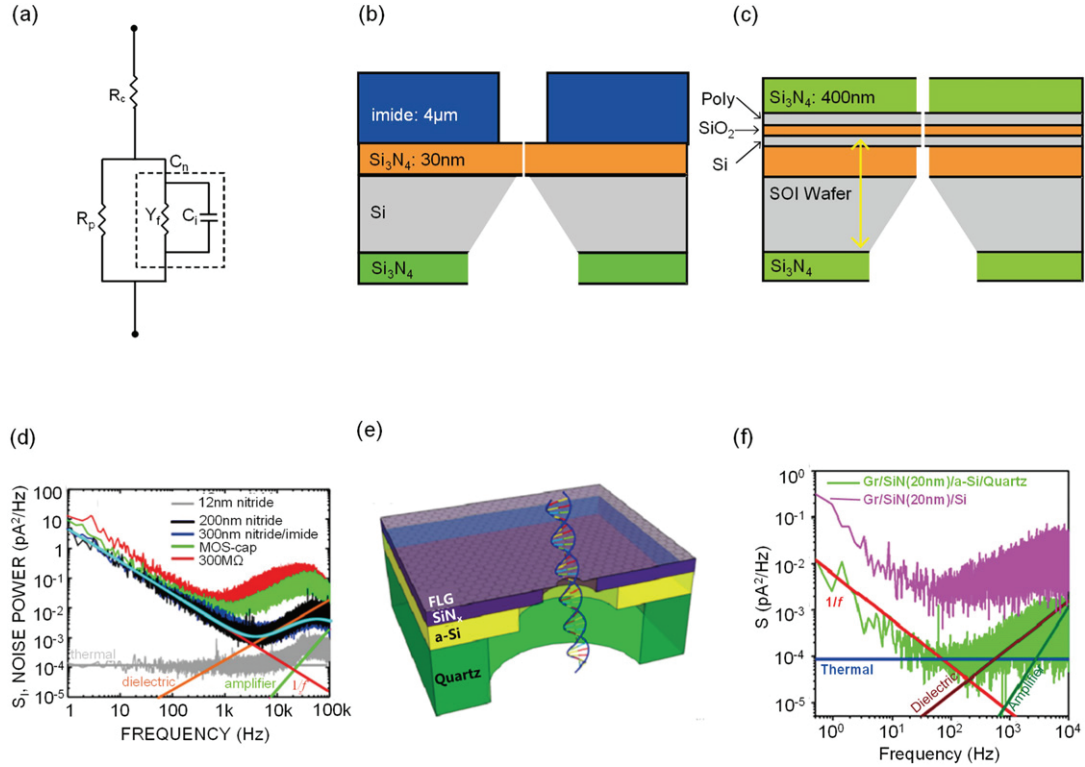
## 5. Dielectric noise

### 5.1. Dielectric noise origin

Dielectric noise is related to dielectric loss due to the non-ideal existence of charge carriers in the dielectric material.<sup>43</sup> In nanopores, while the measured current is exclusively from the ionic current through the nanopore, there is always a leakage current through the non-ideal dielectric membrane (in which charge carriers exist). The thermal fluctuations of this non-ideal leakage current contribute to dielectric noise. To study the dielectric noise induced by non-ideal capacitance  $C_n$ , it can be modeled as an ideal capacitor  $C_i$  in parallel with admittance  $Y_f$  related to the dielectric loss (Fig. 5(a)). Therefore, the dielectric noise can be described as,

$$S_D(f) = 4kT \cdot Y_f = 8\pi kTC_n D \cdot f \quad (11)$$

where  $D$  is the dielectric loss constant. It is clear that material with more loss will have greater dielectric noise.



**Fig. 5.** Model and reduction of dielectric noise. (a) Equivalent circuit model based on Fig. 2(b) for dielectric noise.  $R_e$  ( $=R_{w1} + R_{w2}$ ) is the resistance of two electrolyte cells.  $R_p$  is the resistance from the nanochannel.  $C_n$  represents the non-ideal membrane capacitance, which is the sum of  $C_m$  and  $C_s$  and is expressed in parallel connection of an admittance  $Y_i$  and an ideal capacitance  $C_i$ . (b) A  $\text{SiN}_x$  chip was coated by polyimide. (c) Polysilicon/ $\text{SiO}_2$ /Si (MOS), a multiple-layer structure, was used for nanopore fabrication. (d) The PSD of four different structures, two of which are shown in (b) and (c). (b–d) Redrawing based on reference<sup>52</sup> (Republished with permission of Nanotechnology, from [Nanopores in solid-state membranes engineered for single molecule detection, Dimitrov V et al., 21, 065502 (11pp) 2010]; Permission conveyed through Copyright Clearance Center, Inc.). (e) Schematic of a graphene chip with quartz substrate, connected by a thin Si layer. (f) Noise power spectrum density of two chips with Si or quartz substrate. (e–f) Redrawing based on reference<sup>68</sup> (Republished with permission of Nanotechnology, from [Noise and its reduction in graphene-based nanopore devices, Kumar A et al., 24, 495503 (7pp) 2013]; Permission conveyed through Copyright Clearance Center, Inc.).

## 5.2. Reducing dielectric noise

Based on Eq. (11), the dielectric noise is determined by the total capacitance and dielectric loss constant of the material that isolates the electrolyte. Therefore, two clear approaches can be used to reduce the dielectric noise. One is to reduce the total capacitance, which can be done by covering the nanopore chip with insulation materials (e.g., PDMS<sup>39</sup> and polyimide<sup>52</sup>). Stacked dielectric structures can also be used.<sup>53,82</sup> With these methods, the dielectric noise was reduced by 1–2 orders of magnitude, as shown in Fig. 5(b)–(d). The other approach is to use materials with less loss. Since the Si substrate is often the main source of the dielectric loss, another insulation material can be deposited on the substrate or another substrate can be used. It was experimentally observed that the biological and glass nanopores, in general, have better dielectric noise performances than  $\text{SiN}_x$  and 2D material nanopores, which can be attributed to the latter's high loss factor from the Si substrate. Kumar<sup>68</sup> used quartz as the substrate of graphene nanopores (Fig. 5(e)) and the dielectric noise was significantly decreased (Fig. 5(f)). Other materials, such as Teflon<sup>54</sup> and polyimide,<sup>83</sup> can also be used to replace Si. Clearly, the dielectric noise can be reduced by combining these two approaches. For example, de Vreede<sup>84</sup> nearly completely suppressed the dielectric noise at a wide bandwidth (<100 kHz) using a fused silica substrate and covering it with PDMS.

## 6. Amplifier noise

### 6.1. Amplifier noise origin

In a high-frequency range, the noise PSD is proportional to  $f^2$ , corresponding to the amplifier noise. The amplifier noise comes from the

interactions of thermal noise at the amplifier input and the total capacitance in the system (including capacitances from the chip and the amplifier).<sup>53</sup> The amplifier noise can be expressed as,<sup>33</sup>

$$S_A(f) = (2\pi C_t e_n)^2 \cdot f^2 \quad (12)$$

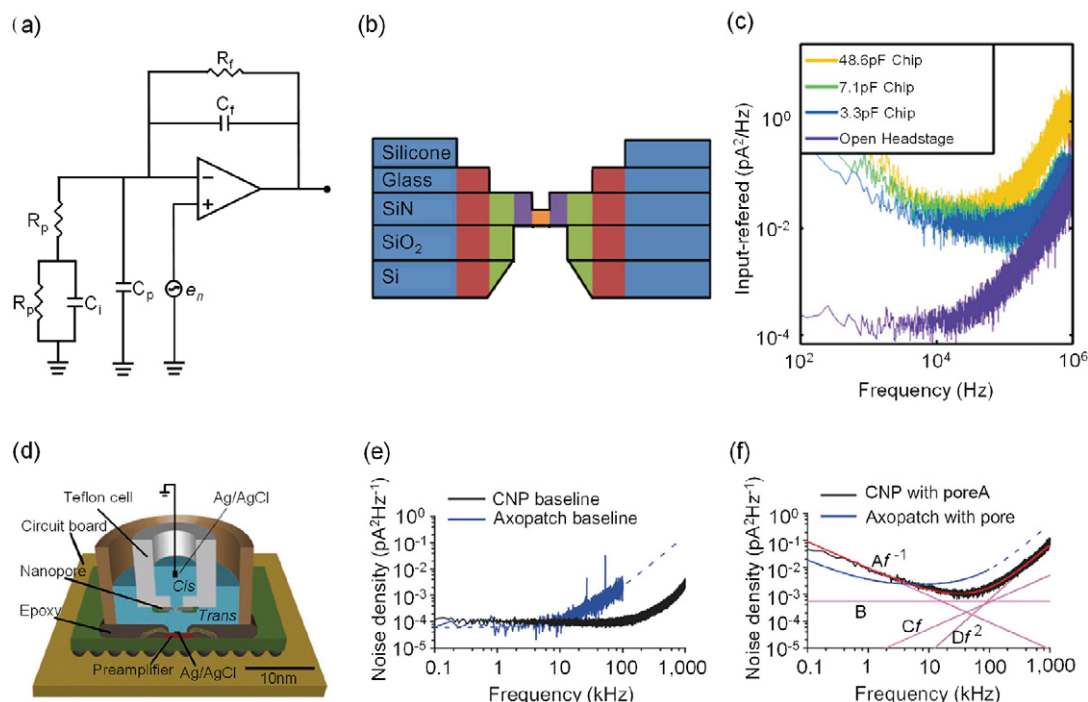
in which  $e_n$  is the voltage thermal noise,  $C_t$  is the total capacitance that consists of the nanopore capacitance ( $C_i$ ), feedback capacitance ( $C_f$ ), and other parasitic capacitance ( $C_p$ ), as shown in Fig. 6(a).

### 6.2. Reducing amplifier noise

According to Eq. (12), the amplifier noise is determined by the total capacitance  $C_t$  and voltage thermal noise,  $e_n$ . Reducing the  $C_t$  is a common practice to suppress the amplifier noise, which can be realized two ways. One is to reduce the nanopore capacitance. For example, replacing the intrinsic  $\text{SiN}_x$  nanopore ( $C_i = 48.6$  pF) with a glass-passivated nanopore chip with  $C_i < 10$  pF<sup>82</sup> (Fig. 6(b)) can greatly reduce the amplifier noise (Fig. 6(c)). The other way is to use amplifiers with low parasitic capacitance ( $C_p$  and  $C_f$ ) as well as reduced voltage thermal noise. For example, replacing the commonly used Axopatch 200B with a CMOS integrated nanopore platform (CNP) (Fig. 6(d))<sup>53</sup> is effective in reducing the amplifier noise (Fig. 6(e) and (f)).

## 7. Material-dependent RMS noise benchmarking

Among the four noise components we discussed, the  $1/f$  and dielectric noise are intrinsic to nanopore materials. To benchmark the noise levels of different materials, we summarized the RMS noise level for biological (Table 1), quartz glass (Table 2),  $\text{SiN}_x$  (Table 3), and 2D material



**Fig. 6.** Model and reduction for amplifier noise. (a) Equivalent circuit model based on Fig. 2(b) for the calculation of amplifier noise.  $R_c$ ,  $R_p$ , and  $C_1$  have the same meaning with symbols in Fig. 5(a).  $R_f$  is the feedback resistance. (b) Schematic diagram of a glass-passivated nanopore chip. (c) Comparison of power spectra density of two glass-passivated chips (3.3 pF and 7.1 pF) and a non-passivated chip (48.6 pF). (b–c) Redrawing based on reference<sup>82</sup> (Reprinted with permission from [Balan A, Machiels B, Niedzwiecki D, et al. Improving signal-to-noise performance for DNA translocation in solid-state nanopores at MHz bandwidths. *Nano Letters* 2014;14(12):7215–7220.]. Copyright (2014) American Chemical Society.). (d) Schematic diagram of the measurement setup of CNP platform. (e) Comparison of the baseline noise spectrum of a similar open-headstage configuration connecting with CNP and Axopatch 200B. (f) Comparison of the noise power spectra of nanopores when tested by CNP and Axopatch 200B. (d–f) Redrawing based on reference<sup>53</sup> (Reprinted by permission from [Springer Nature Customer Service Centre GmbH]; [Springer Nature] [Nature Methods] [Integrated nanopore sensing platform with sub-microsecond temporal resolution, Rosenstein JK et al.], [COPYRIGHT] (2012)).

(Table 4) nanopores. The  $I_{rms}$  values in Tables 1–4 were calculated from the reported PSD data using Eq. (4), or based on the reported  $I_{rms}$  data acquired directly from the text or chart, within the same bandwidth from 1 Hz to 10 kHz for a fair comparison. Fig. 7 shows the RMS noise

scattering plot as a function of the nanopore materials. The noise level in the SiN<sub>x</sub> nanopore and 2D material nanopore is greater than that in the glass nanopore, while the biological nanopores show the best noise performance. The two populations in the quartz glass nanopore

**Table 1**  
Noise level statistic of biological nanopores.

Structure	$I_{rms}$ (pA)	Diameter (nm)	Ionic strength (Molar)	pH	Bias (mV)	Ref.
$\alpha$ -Hemolysin	2.70	n.a.	1.00	8.00	200	39
	2.51	1.4	0.20	7.40	100	86
	2.49	1.4	0.20	7.40	0	86
	4.47	1.4	1.00	3.50	100	86
	2.13	1.4	1.00	3.50	0	86
FhuA $\Delta C/\Delta 4L$	2.69	3.1–4.4	0.20	7.40	100	86
	2.49	3.1–4.4	0.20	7.40	0	86
	2.13	3.1–4.4	1.00	3.50	0	86
	2.08	3.8	0.15	7.50	35	87
	2.07	3.8	0.15	7.50	–35	87
ClyA	2.07	3.8	0.15	7.50	0	87

**Table 2**  
Noise level statistic of quartz-based glass nanopores.

Structure	$I_{rms}$ (pA)	Diameter (nm)	Ionic strength (Molar)	pH	Bias (mV)	Ref.
Bare nanopore	3.09	25.0	0.001	n.a.	–500	88
	1.79	75.0 $\pm$ 5.0	1.00	8.0	300	85
	27.06	21.0	1.00	8.0	2000	76
	24.90	23.0	1.00	8.0	2000	76
	2.91	15.0	0.001	n.a.	–500	88
Au deposited	17.35	59.0 $\pm$ 5.0	1.00	8.0	300	85
	16.72	47.0 $\pm$ 5.0	1.00	8.0	300	85
	20.11	41.0 $\pm$ 5.0	1.00	8.0	300	85

**Table 3**  
Noise level statistic of SiN<sub>x</sub> nanopores.

Structure	$I_{rms}$ (pA)	Diameter (nm)	Ionic strength (Molar)	pH	Bias (mV)	Ref.
Bare SiN <sub>x</sub>	45.58	n/a	1.00	8.0	200	39
	63.20	20.0	1.00	8.0	100	89
	48.10	20.0	1.00	8.0	100	89
	90.47	20.8	1.00	7.5	100	44
	27.07	22.0	1.00	7.5	100	44
	147.00	n/a	1.00	8.0	0	83
	27.10	3.3–4.0	1.00	8.0	100	52
	131.60	n/a	1.00	8.0	4.5	54
					(nA) <sup>a</sup>	
	38.00	n/a	1.00	8.0	0	54
Bare SiN <sub>x</sub> with zapping treatment	21.90	n/a	1.00	8.0	200	39
	28.60	7.0	1.00	8.0	200	64
	13.60	7.0	1.00	8.0	200	64
	14.40	21.0	1.00	8.0	200	64
PDMS coated	6.45	n/a	1.00	8.0	200	39
PI coated	6.40	1.7–2.8	1.00	8.0	100	52
MOS-cap <sup>b</sup>	6.40	7.1–7.3	1.00	8.0	100	52
SiO <sub>2</sub> coated	33.10	20.0	1.00	8.0	100	89
	24.50	20.0	1.00	8.0	100	89
	28.30	20.0	1.00	8.0	100	89
Stacked	7.11	n/a	1.00	8.0	n/a	53
Glass-passivated stacked	16.37	n/a	1.00	8.0	n/a	82
	23.36	n/a	1.00	8.0	n/a	82
PI substrate	5.40	n/a	1.00	8.0	0	83
Quartz substrate	12.58	n/a	1.00	8.0	4.5	54
					(nA) <sup>a</sup>	

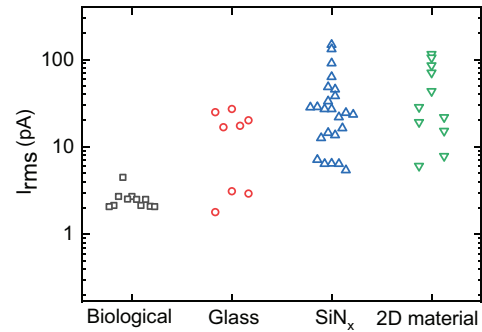
<sup>a</sup> Driven by constant current.<sup>b</sup> MOS-cap means the SiN<sub>x</sub> membrane was replaced by a MOS structure.

were mainly due to (1) the difference between the bare nanopore and surface-coated nanopores,<sup>85</sup> and (2) the different experimental conditions.

Material-related RMS noise is related to the  $1/f$  noise and dielectric noise dominating the total noise. From the  $1/f$  noise perspective, it is reasonable to hypothesize that different types of nanopores have different surface properties (e.g., surface charge, roughness, and hydrophilicity), geometry, and membrane stability, corresponding to varying levels of  $1/f$  noise. For example, glass nanopores have better hydrophilicity and show less  $1/f$  noise than the SiN<sub>x</sub> nanopore. SiN<sub>x</sub> nanopores are generally fabricated by TEM or focused ion beam (FIB) during which surface roughness, trapped electrons, or ions could be introduced. The low hydrophilicity of the SiN<sub>x</sub> surface may produce nanobubbles more easily than biological and glass nanopores, and may produce more pronounced  $1/f$  noise. Nanopores based on 2D materials have a higher  $1/f$  noise level than other nanopore types, most likely due to mechanical vibrations. In addition, from the dielectric noise perspective, the dielectric loss of the Si substrate would introduce relatively large dielectric noise to SiN<sub>x</sub> and 2D material nanopores.

**Table 4**  
Noise level statistic of a nanopore based on a 2D material.

Structure	$I_{rms}$ (pA)	Diameter (nm)	Ionic strength (Molar)	pH	Bias (mV)	Ref.
Bare graphene	115.39	4.0	1.0	8.0	100	71
	104.93	10.0	1.0	8.1	100	69
	85.79	8.0	1.0	9.0	100	78
Graphene deposited TiO <sub>2</sub>	7.87	7.5	1.0	9.0	100	78
Graphene on quartz	70.45	6.0	1.0	8.0	100	68
Multilayer graphene on quartz	21.80	5.0	1.0	8.0	100	68
h-BN	43.46	n/a	1.0	7.8	n/a	90
	28.55	5.0	1.0	8.0	100	72
h-BN on pyrex	15.26	4.0	1.0	8.0	100	72
h-BNs on pyrex	6.06	8.0	1.0	8.0	100	72
MoS <sub>2</sub>	19.15	2.8	0.4	8.0	100	80

**Fig. 7.** Comparison of  $I_{rms}$  (integrated from 1 Hz to 10 kHz) for different types of nanopores (data from Tables 1–4).

## 8. Conclusion and future prospects

In summary, we reviewed and summarized the physical models, origins, and reduction methods for four noise components in nanopore sensors ( $1/f$  noise, white noise, dielectric noise, and amplifier noise). For the first time, we calculated and benchmarked the RMS values for different types of nanopores. There is a clear material-specific noise characteristic for nanopore sensors. Biological and glass nanopores show less RMS noise than SiN<sub>x</sub> and 2D material nanopores. There are still many unknowns of nanopore noise. The exact origin of the noise, especially the origin of  $1/f$  noise, is still not clear. Without pinpointing the exact noise origins, the noise reduction effort can only be performed by an “error-and-try” approach. We need more theoretical and experimental work in this area. For example, it was previously observed that the nanopore noise can be conditioned by applying an electric field, however, the physical mechanisms of this “conditioning” remain unknown. In addition, we need to develop deeper insight into the impact of nanopore surface properties on the noise performances to control and modify its property. Fabrication methods beyond TEM and FIB may reduce the defect states in the pore-forming material (for reducing the dielectric noise). Lastly, we need to develop high performance, nanopore-integrated amplifiers to reduce the amplifier noise. We anticipate this review article will enhance our understanding of the impact of material properties on the nanopore noise and provide an informative tutorial into developing future nanopore sensors with a high SNR.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.



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## References

- Clarke J, Wu HC, Jayasinghe L, et al. Continuous base identification for single-molecule nanopore DNA sequencing. *Nat Nanotechnol* 2009;4(4):265–70.
- Garaj S, Liu S, Golovchenko JA, et al. Molecule-hugging graphene nanopores. *Proc Natl Acad Sci U S A* 2013;110(30):12192–6.
- Plesa C, Kowalczyk SW, Zinsmeister R, et al. Fast translocation of proteins through solid state nanopores. *Nano Lett* 2013;13(2):658–63.
- Li JL, Stein D, Qun C, et al. Solid state nanopore as a single DNA molecule detector. *Biophys J* 2003;84(2):134a–5a.
- Lua RC, Grosberg AY. First passage times and asymmetry of DNA translocation. *Phys Rev E* 2005;72(6):061918.
- Heins EA, Siwy ZS, Baker LA, et al. Detecting single porphyrin molecules in a conically shaped synthetic nanopore. *Nano Lett* 2005;5(9):1824–9.
- Storm AJ, Chen JH, Zandbergen HW, et al. Translocation of double-strand DNA through a silicon oxide nanopore. *Phys Rev E* 2005;71(5):051903.
- Storm AJ, Storm C, Chen JH, et al. Fast DNA translocation through a solid-state nanopore. *Nano Lett* 2005;5(7):1193–7.
- Fologea D, Gershow M, Ledden B, et al. Detecting single stranded DNA with a solid state nanopore. *Nano Lett* 2005;5(10):1905–9.
- Yan H, Xu BQ. Towards rapid DNA sequencing: detecting single-stranded DNA with a solid-state nanopore. *Small* 2006;2(3):310–2.
- Keyser UF, Koelman BN, Van Dorp S, et al. Direct force measurements on DNA in a solid-state nanopore. *Nat Phys* 2006;2(7):473–7.
- Healy K. Nanopore-based single-molecule DNA analysis. *Nanomedicine* 2007;2(4):459–81.
- Branton D, Deamer DW, Marziali A, et al. The potential and challenges of nanopore sequencing. *Nat Biotechnol* 2008;26(10):1146–53.
- Talaga DS, Li JL. Single-molecule protein unfolding in solid state nanopores. *J Am Chem Soc* 2009;131(26):9287–97.
- Wanunu M, Sutin J, Meller A. DNA profiling using solid-state nanopores: detection of DNA-binding molecules. *Nano Lett* 2009;9(10):3498–502.
- Wanunu M, Morrison W, Rabin Y, et al. Electrostatic focusing of unlabelled DNA into nanoscale pores using a salt gradient. *Nat Nanotechnol* 2010;5(2):160–5.
- Venkatesan BM, Bashir R. Nanopore sensors for nucleic acid analysis. *Nat Nanotechnol* 2011;6(10):615–24.
- Wei RS, Gatterdam V, Wieneke R, et al. Stochastic sensing of proteins with receptor-modified solid-state nanopores. *Nat Nanotechnol* 2012;7(4):257–63.
- Lin Y, Ying YL, Shi X, et al. Direct sensing of cancer biomarkers in clinical samples with a designed nanopore. *Chem Commun* 2017;53(84):11564–7.
- Sha J, Si W, Xu B, et al. Identification of spherical and nonspherical proteins by a solid-state nanopore. *Anal Chem* 2018;90(23):13826–31.
- Goto Y, Yanagi I, Matsui K, et al. Identification of four single-stranded DNA homopolymers with a solid-state nanopore in alkaline CsCl solution. *Nanoscale* 2018;10(44):20844–50.
- Yang H, Li Z, Si W, et al. Identification of single nucleotides by a tiny charged solid-state nanopore. *J Phys Chem B* 2018;122(32):7929–35.
- Bello EC, Mowla M, Troise N, et al. Increased dwell time and occurrence of dsDNA translocation events through solid state nanopores by LiCl concentration gradients. *Electrophoresis* 2019;40(7):1082–90.
- Wang J, Yang J, Ying YL, et al. Nanopore-based confined spaces for single-molecular analysis. *Chem Asian J* 2018;14(3):389–97.
- Rivas F, Zahid OK, Reesink HL, et al. Label-free analysis of physiological hyaluronan size distribution with a solid-state nanopore sensor. *Nat Commun* 2018;9(1):1037.
- Plesa C, Verschueren D, Pud S, et al. Direct observation of DNA knots using a solid-state nanopore. *Nat Nanotechnol* 2016;11(12):1093–7.
- Yusko EC, Bruhn BR, Eggenberger OM, et al. Real-time shape approximation and fingerprinting of single proteins using a nanopore. *Nat Nanotechnol* 2017;12(4):360–7.
- Kasianowicz JJ, Brandin E, Branton D, et al. Characterization of individual polynucleotide molecules using a membrane channel. *Proc Natl Acad Sci U S A* 1996;93(24):13770–3.
- Derrington IM, Butler TZ, Collins MD, et al. Nanopore DNA sequencing with MspA. *Proc Natl Acad Sci U S A* 2010;107(37):16060–5.
- Jain M, Olsen HE, Paten B, et al. The Oxford Nanopore MinION: delivery of nanopore sequencing to the genomics community. *Genome Biol* 2016;17(1):239.
- Jain M, Koren S, Miga KH, et al. Nanopore sequencing and assembly of a human genome with ultra-long reads. *Nat Biotechnol* 2018;36(4):338–45.
- Albrecht T. Single-molecule analysis with solid-state nanopores. *Annu Rev Anal Chem* 2019;12(1):371–87.
- Lee K, Park KB, Kim HJ, et al. Recent progress in solid-state nanopores. *Adv Mater* 2018;30(42):1704680.
- Li J, Stein D, McMullan C, et al. Ion-beam sculpting at nanometre length scales. *Nature* 2001;412(6843):166–9.
- Roshan KA, Tang Z, Guan W. High fidelity moving Z-score based controlled breakdown fabrication of solid-state nanopore. *Nanotechnology* 2019;30(9):095502.
- Chen W, Liu G-C, Ouyang J, et al. Graphene nanopores toward DNA sequencing: a review of experimental aspects. *SCIENCE CHINA Chem* 2017;60(6):721–9.
- Zhang SD, Li MZ, Su B, et al. Fabrication and use of nanopipettes in chemical analysis. *Annu Rev Anal Chem* 2018;11(1):265–86.
- Mara A, Siwy Z, Trautmann C, et al. An asymmetric polymer nanopore for single molecule detection. *Nano Lett* 2004;4(3):497–501.
- Tabard-Cossa V, Trivedi D, Wiggin M, et al. Noise analysis and reduction in solid-state nanopores. *Nanotechnology* 2007;18(30):305505.
- Manrao EA, Derrington IM, Laszlo AH, et al. Reading DNA at single-nucleotide resolution with a mutant MspA nanopore and phi29 DNA polymerase. *Nat Biotechnol* 2012;30(4):349–53.
- Nouri R, Tang ZF, Guan WH. Calibration-free nanopore digital counting of single molecules. *Anal Chem* 2019;91(17):11178–84.
- Schneider GF, Xu Q, Hage S, et al. Tailoring the hydrophobicity of graphene for its use as nanopores for DNA translocation. *Nat Commun* 2013;4(1):2619.
- Uram JD, Ke K, Mayer M. Noise and bandwidth of current recordings from submicrometer pores and nanopores. *ACS Nano* 2008;2(5):857–72.
- Smeets RMM, Keyser UF, Dekker NH, et al. Noise in solid-state nanopores. *Proc Natl Acad Sci U S A* 2008;105(2):417–21.
- Smeets RMM, Dekker NH, Dekker C. Low-frequency noise in solid-state nanopores. *Nanotechnology* 2009;20(9):095501.
- Hoogerheide DP, Garaj S, Golovchenko JA. Probing surface charge fluctuations with solid-state nanopores. *Phys Rev Lett* 2009;102(25):256804.
- Parkin WM, Drndic M. Signal and noise in FET-nanopore devices. *ACS Sens* 2018;3(2):313–9.
- Albu M, Heydt GT. On the use of RMS values in power quality assessment. *IEEE Trans Power Delivery* 2003;18(4):1586–7.
- Dutta P, Horn PM. Low-frequency fluctuations in solids: 1/f noise. *Rev Mod Phys* 1981;53(3):497–516.
- Hartel AJW, Shekar S, Ong P, et al. High bandwidth approaches in nanopore and ion channel recordings – a tutorial review. *Anal Chim Acta* 2019;1061:13–27.
- Siwy Z, Fulinski A. 1/f noise in ion transport through nanopores: origins and mechanisms. In: Bezrukov SM, ed. *Unsolved problems of noise and fluctuations*. Melville: Amer Inst Physics; 2003. p. 273–82.
- Dimitrov V, Mirsaidov U, Wang D, et al. Nanopores in solid-state membranes engineered for single molecule detection. *Nanotechnology* 2010;21(6):065502.
- Rosenstein JK, Wanunu M, Merchant CA, et al. Integrated nanopore sensing platform with sub-microsecond temporal resolution. *Nat Methods* 2012;9(5):487–92.
- Lee MH, Kumar A, Park KB, et al. A low-noise solid-state nanopore platform based on a highly insulating substrate. *Sci Rep* 2014;4:7448.
- Waggoner PS, Kuan AT, Polonsky S, et al. Increasing the speed of solid-state nanopores. *J Vac Sci Technol B* 2011;29(3):032206.
- Van Der Ziel A. On the noise spectra of semi-conductor noise and of flicker effect. *Physica* 1950;16(4):359–72.
- Costanzi BN, Dahlberg ED. Emergent 1/f noise in ensembles of random telegraph noise oscillators. *Phys Rev Lett* 2017;119(9):097201.
- Powell MR, Vlassioulis I, Martens C, et al. Nonequilibrium 1/f noise in rectifying nanopores. *Phys Rev Lett* 2009;103(24):248104.
- Fragasso A, Pud S, Dekker C. 1/f noise in solid-state nanopores is governed by access and surface regions. *Nanotechnology* 2019;30(39):395202.
- Siwy Z, Fulinski A. Origin of 1/f(alpha) noise in membrane channel currents. *Phys Rev Lett* 2002;89(15):158101.
- Bezrukov SM, Winterhalter M. Examining noise sources at the single-molecule level: 1/f noise of an open maltoporin channel. *Phys Rev Lett* 2000;85(1):202–5.
- Smeets RMM, Keyser UF, Wu MY, et al. Nanobubbles in solid-state nanopores. *Phys Rev Lett* 2006;97(8):088101.
- Roth R, Gillespie D, Nonner W, et al. Bubbles, gating, and anesthetics in ion channels. *Biophys J* 2008;94(11):4282–98.
- Beamish E, Kwok H, Tabard-Cossa V, et al. Precise control of the size and noise of solid-state nanopores using high electric fields. *Nanotechnology* 2012;23(40):405301.
- Tasserit C, Koutsoubas A, Lairez D, et al. Pink noise of ionic conductance through single artificial nanopores revisited. *Phys Rev Lett* 2010;105(26):260602.
- Gravelle S, Netz RR, Bocquet L. Adsorption kinetics in open nanopores as a source of low-frequency noise. *Nano Lett* 2019;19(10):7265–72.
- Radenovic A, Trepagnier E, Csencsits R, et al. Fabrication of 10 nm diameter hydrocarbon nanopores. *Appl Phys Lett* 2008;93(18):183101.
- Kumar A, Park KB, Kim HM, et al. Noise and its reduction in graphene based nanopore devices. *Nanotechnology* 2013;24(49):495503.
- Heerema SJ, Schneider GF, Rozemuller M, et al. 1/f noise in graphene nanopores. *Nanotechnology* 2015;26(7):074001.
- Arjmandi-Tash H, Belyaeva LA, Schneider GF. Single molecule detection with graphene and other two-dimensional materials: nanopores and beyond. *Chem Soc Rev* 2016;45(3):476–93.
- Zhang ZY, Deng YS, Tian HB, et al. Noise analysis of monolayer graphene nanopores. *Int J Mol Sci* 2018;19(9):2639.
- Park KB, Kim HJ, Kim HM, et al. Noise and sensitivity characteristics of solid-state nanopores with a boron nitride 2-D membrane on a pyrex substrate. *Nanoscale* 2016;8(10):5755–63.



73. Bezrukov SM, Kasianowicz JJ. Current noise reveals protonation kinetics and number of ionizable sites in an open protein ion channel. *Phys Rev Lett* 1993;70(15):2352–5.
74. Wen C, Zeng SS, Arstila K, et al. Generalized noise study of solid-state nanopores at low frequencies. *ACS Sens* 2017;2(2):300–7.
75. Perry D, Momotenko D, Lazenby RA, et al. Characterization of nanopipettes. *Anal Chem* 2016;88(10):5523–30.
76. Steinbock LJ, Bulushev RD, Krishnan S, et al. DNA translocation through low-noise glass nanopores. *ACS Nano* 2013;7(12):11255–62.
77. Powell MR, Martens C, Siwy ZS. Asymmetric properties of ion current 1/f noise in conically shaped nanopores. *Chem Phys* 2010;375(2):529–35.
78. Merchant CA, Healy K, Wanunu M, et al. DNA translocation through graphene nanopores. *Nano Lett* 2010;10(8):2915–21.
79. Chen P, Mitsui T, Farmer DB, et al. Atomic layer deposition to fine-tune the surface properties and diameters of fabricated nanopores. *Nano Lett* 2004;4(7):1333–7.
80. Waduge P, Bilgin I, Larkin J, et al. Direct and scalable deposition of atomically thin low-noise MoS<sub>2</sub> membranes on apertures. *ACS Nano* 2015;9(7):7352–9.
81. Saleh OA, Sohn LL. Quantitative sensing of nanoscale colloids using a microchip Coulter counter. *Rev Sci Instrum* 2001;72(12):4449–51.
82. Balan A, Machielse B, Niedzwiecki D, et al. Improving signal-to-noise performance for DNA translocation in solid-state nanopores at MHz bandwidths. *Nano Lett* 2014;14(12):7215–20.
83. Choi W, Jeon ES, Chun KY, et al. A low-noise silicon nitride nanopore device on a polymer substrate. *PLoS One* 2018;13(7), e0200831.
84. de Vreede LJ, Ying CF, Houghtaling J, et al. Wafer-scale fabrication of fused silica chips for low-noise recording of resistive pulses through nanopores. *Nanotechnology* 2019;30(26), 265301.
85. Sze JYY, Kumar S, Ivanov AP, et al. Fine tuning of nanopipettes using atomic layer deposition for single molecule sensing. *Analyst* 2015;140(14):4828–34.
86. Mohammad MM, Iyer R, Howard KR, et al. Engineering a rigid protein tunnel for biomolecular detection. *J Am Chem Soc* 2012;134(22):9521–31.
87. Soskine M, Biesemans A, Moeyaert B, et al. An engineered ClyA nanopore detects folded target proteins by selective external association and pore entry. *Nano Lett* 2012;12(9):4895–900.
88. Freedman KJ, Otto LM, Ivanov AP, et al. Nanopore sensing at ultra-low concentrations using single-molecule dielectrophoretic trapping. *Nat Commun* 2016;7(1), 10217.
89. Janssen XJ, Jonsson MP, Plesa C, et al. Rapid manufacturing of low-noise membranes for nanopore sensors by trans-chip illumination lithography. *Nanotechnology* 2012;23(47), 475302.
90. Zhou Z, Hu Y, Wang H, et al. DNA translocation through hydrophilic nanopore in hexagonal boron nitride. *Sci Rep* 2013;3:3287.